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ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

| EXAMINER | |
|---|---|
| WOLLENBERGER, LOUIS V | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/978,632 | RABBANI ET AL. | |
| | Examiner | Art Unit | |
| | Louis Wollenberger | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 November 2008 and 08 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *246-252,255,264,265 and 271-275* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *246-252, 255, 264, 265, and 271-275* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/2008, 1/11/2008, 1/10/2008 (2)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 7/8/2008 to the Non-Final Rejection mailed 1/8/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 3/19/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicant's amendments to the claims filed 11/10/2008 have been entered into the application. With entry of the amendment, Claims 246-252, 255, 264, 265, and 271-275 are pending and examined herein.

### *Election/Restrictions*

Applicant's elections with traverse in the reply filed on 11/10/2008 are acknowledged.

Applicant has elected the following:

1. modified nucleotide
2. at least one modified nucleotide with a fusogenic protein and at least one modified nucleotide with a ligand
3. RNA product
4. circular portion
5. double stranded portion
6. construct comprises DNA
7. at least one nucleotide analog is modified on the side chain
8. a sequence complementary to a construct tail

9. the ligand is a small molecule

10. a saccharide non-nucleic acid entity

11. nuclear localization

12. cellular targeting

*Reply to Arguments:*

In general, Applicant argues it would not be an undue burden to search and consider each alternative construct. The Examiner respectfully disagrees, since each construct would require consideration of at least double patenting, utility, written description, enablement, novelty, and obviousness. With regard to the Markush alternatives, the Examiner, therefore, does not agree that they are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden. Each additional limitation requires an additional search and consideration. The examiner has noted, however, that in applications containing a Markush-type claim that encompasses at least two independent or distinct inventions, the examiner may require a provisional election of a single species prior to examination on the merits (MPEP 803.02). Accordingly, the previous requirement mailed 10/8/2008 is considered to be an election of related but distinct species. The species are structurally and functionally distinct for the reasons stated in the Requirement. Applicant's arguments to the contrary have been considered but are not found persuasive, since the species are claimed in the alternative, and at least on their face have structurally distinct features. Even if such features could be combined no such species is claimed, and applicant does not point to any such species in the specification that would provide a starting point for any such search. Further, it is clear that certain species comprise mutually exclusive features, such as claim 248 (single,

double, or triple stranded), claim 265 (macro- or small molecules), and claim 271 (saccharide or polypeptide).

Independent claims 246, 271, and 273 may be generic to species recited in claims depending thereon. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

More specifically, in traversing the election in 1, above, Applicant states modified nucleotides are always nucleotide analogs. Accordingly, the restriction between modified nucleotides and nucleotide analogs is withdrawn.

In other instances, Applicant argues the alternatives have similar functions. This is not persuasive because a similar function does not necessarily require a similar or identical structure, which is essential to the consideration of patentability.

To the extent the Requirement is considered an election to a single species, the requirement is still deemed proper and is therefore made FINAL.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 246-252, 255, 264, 265, and 271-275 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 245-248, 251, 253, 261-265, 306, and 307 of copending Application No. 08/978,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting application 08/978,633 claims a nucleic acid construct and composition thereof comprising a polynucleotide tail, an antibody, and a chemical modification or a ligand.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the reply filed 7/8/2008, Applicant states the provisional rejection will be addressed once there is an indication of allowable subject matter. The reply does not present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references (37 CFR 1.111(b)).

The Examiner notes allowable subject matter has not yet been identified. Accordingly, the provisional rejection is maintained for the reasons of record, reiterated above.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 246-252, 255, 264, 265, and 271-275 are rejected under 35 U.S.C. 102(e) as being anticipated by Craig et al. (US Patent 5,766,902).

*Response to Applicant's arguments:*

Applicant's arguments filed 7/8/2008 have been fully considered but are not persuasive. Claim 246 recites the limitation "wherein at least one modified nucleotide or nucleotide analog comprises a fusogenic protein and at least one modified nucleotide or nucleotide analog comprises a ligand…" Page 41 of the specification states:

Ligands or chemical modifications, being any chemical entity, natural or synthetic, which can be utilized in this invention include macromolecules greater than 20,000 m.w. as well as small molecules less that 20,000 m.w. The ligand or ligands can include both macromolecules and small molecules. Macromolecules which can be utilized include a variety of natural and synthetic polymers inlcluding peptides and proteins, nucleic acids, polysaccharides, lipids, synthetic polymers including polyanions, polycations, and mixed polymers. Small molecules include oligopeptides, oligonucleotides, monosaccharides, oligosaccharides and synthetic polymers including polyanions, polycations, lipids and mixed polymers. Small molecules include mononucleotides, oligonucleotides, oligopeptides, oligosaccharides, monosaccharides, lipids, sugars, and other natural and synthetic entities.

Ligands and chemical modifications provide useful properties for nucleic acid transfer such as 1) cell targeting entities, 2) entities which facilitate cellular uptake, 3) entities specifying intracellular localization, 4) entities which facilitate incorporation into cellular nucleic acid and 5) entities which impart nuclease resistance.

Page 42 of the specification states:

1) Cell targeting entities which can be utilized include:

a) antibodies to cellular surface components and epitopes

b) viruses, virus components or fragments of virus components which have affinity for cellular surface components. These include such proteins as the gp120 protein of HIV which binds to the CD4 receptor of T4 lymphocytes (Lever 1995 British Medical Bulletin **51**;149, incorporated herein by reference).

c) ligands which have affinity for cell surfaces. These include hormones, lectins, proteins, oligosaccharides and polysaccharides. Asialoorosomucoid, for example, binds to the cellular asialoglycoprotein receptor (Wu et al. 1989 J Biol Chem **269**;16985, incorporated herein by reference) and transferrin binds to transferrin cellular receptors (Wagner et al. 1992 89; 6099, also incorporated herein by reference).

Page 43 states:

e) Matrix proteins such as fibronectin that bind to hematopoietic cells and other cells (Ruoslahti et al. 1981 J. Biol. Chem. **256**;7277, incorporated by reference),

f) lectins which bind to cell surface components.

Entities which facilitate cellular uptake include inactivated viruses such as adenovirus (Cristiano et al. 1993 Proc Natl Acad Sci USA **90**;2122: Curiel et al. 1991 Proc Natl Acad Sci USA **88**;8850, all of which are incorporated by reference); virus components such as the hemaglutinating protein of influenza virus and a peptide fragment from it, the hemagglutinin HA-2 N-terminal fusogenic peptide (Wagner et al. 1992 Proc Natl Acal USA **89**;7934, also incorporated herein by reference).

Accordingly, the term "ligand" as used by the instant claims would appear to reasonably embrace both small and large molecules, proteins and peptides, entities that impart nuclease resistance as well as those that facilitate cellular targeting. Therefore, the distinction between the term "ligand" and "fusogenic protein," if any, is unclear. A fusogenic protein such as any of those defined by the art is reasonably also considered to be a "ligand" within the scope of the claims. The claims do not require the fusogenic protein be different from the ligand or that two types of ligands be present in the construct. The claims merely require a ligand and a fusogenic protein. Given that fusogenic protein is a ligand, according to the specification, constructs comprising fusogenic proteins necessarily comprise a ligand. Therefore, Applicant argues a

limitation not present in the claims. As acknowledged by Applicant at page 11 of the Remarks, Craig et al. disclosed that a DNA construct may be associated with a fusogenic protein (see column 8 of Craig et al.)

*The rejection:*

Craig et al. taught methods for enhancing the targeted delivery of nucleic acid molecules to cells by coupling the nucleic acid to a ligand having affinity for a cell surface molecule or receptor. The ligand facilitates uptake of the nucleic acid by receptor mediated endocytosis (cols. 2-6). The nucleic acid molecule preferably comprises at least one transcription unit encoding a protein or RNA molecule such as an antisense oligonucleotide or ribozyme (col. 3, lines 59-62; col. 4, lines 24-28). The nucleic acid molecule may be plasmid DNA or a recombinant viral genome, such as any adenoviral or retroviral vector (col. 12, lines 1-25). Thus, the types of nucleic acids contemplated for use with the invention include single and double stranded, linear and circular, DNA and RNA molecules. The ligand may be any molecule, small or large, capable of binding to a cell and/or facilitating delivery into the cell (col. 4, lines 29-45), including proteins, carbohydrates, and metal ions. Specifically recommended are antibodies, growth factors, and fusogenic peptides (col. 4 and 8). The ligand may be chemically conjugated by covalent bonded to the nucleic acid (col. 8, lines 14-15). Covalent conjugation would necessarily result in modification of the sugar, phosphate, or nucleobase portion of one or more nucleotides of the nucleic acid. Therefore, the construct would comprise a modified nucleotide and nucleotide analog, since, according to Applicant, modified nucleotides are nucleotide analogs. As acknowledged by Applicant at page 11 of the Remarks, Craig et al. disclosed that a DNA

construct may be associated with a fusogenic protein (see column 8 of Craig et al.). Specifically, Craig et al. stated that "Delivery of the foreign DNA into the target cell may also be achieved via the DNA construct's association with an endosomal disruption agent, such as the influenza hemagglutinin fusogenic peptide." As evidenced by pages 41-43 of the specification, fusogenic proteins, such as the hemaglutinating protein of influenza virus, are ligands.

With regard to claim 255, the constructs disclosed by Craig et al. would necessarily require modifying a portion of a nucleotide, which portion must necessarily be the backbone or "side chain." (It is noted the limitation "side chain" is not an art-recognized term for the description of nucleotide regions, and it is unclear exactly what feature of a nucleic acid is meant by "side chain." The term "side chain" is more often used to describe amino acids.).

Accordingly, Craig et al. taught a construct of the type defined by the claims, including new claims 271-275, since Craig et al. disclosed constructs comprising ligands that are polypeptides that confer cell targeting and cellular localization (e.g., ligands that localize the construct to a cell, such as antibodies), because in such constructs the polypeptide would necessarily be conjugated to one strand, and because Craig et al. taught using such methods with viral (i.e., linear) and plasmid (i.e., circular genomes). Insofar as Claim 273, the limitation "polynucleotide tail", as noted above, since the claim actually requires the tail be hybridized to a complementary sequences. There would appear to be no single stranded tail therefor.

Accordingly, Craig et al. anticipates the invention as now claimed.

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Claims 246-249, 252, 255, 264, 265, and 274 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirsch et al. (1993) *Transplantation Proceedings* 25:138-139.

*Response to Arguments:*

Applicant's arguments filed 7/8/2008 have been fully considered but are not persuasive insofar as claims 246-249, 252, 255, 264, and 265. As explained above, there is no clear distinction between ligands and fusogenic proteins. The term "ligand" embraces fusogenic proteins. Fusogenic proteins are ligands as defined by the specification. See pages 41-43. Further, page 42 of the specification clearly teaches antibodies to cell surface components and epitopes are ligands. The claims do not require two different ligands or fusogenic proteins. Furthermore, neither the claims nor the specification provide a clear limiting definition of the term "fusogenic protein." It is therefore unclear as to which proteins are specifically included or excluded by the term "fusogenic protein." In the absence of any clear indication from the specification as what does or does not constitute a fusogenic protein, the monoclonal antibody of Hirsch et al. is considered to represent a fusogenic protein (and thereby a ligand) since it promotes binding and thereby fusion between a nucleic acid construct and a cell. To the extent the antibody localizes or targets the nucleic acid construct to the cell, it, similarly, serves as a cellular localization signal. Accordingly, Hirsch et al. continues to anticipate the claims for the reasons of record, reiterated below, since Hirsch et al. taught a construct comprising a fusogenic protein, and, therefore, a ligand. The covalent linkage to a nucleotide produces, by definition, a modified nucleotide.

*The rejection:*

Hirsch et al. taught a method for the targeted transfection of plasmid DNA, comprising covalently coupling the DNA to a monoclonal antibody. In one example, the plasmid DNA encodes the neomycin resistance gene Fig. 1 and results, pp 138-9). It is said the conjugated

plasmid is effectively transfected into cells and can result in stable long term expression of the encoded gene. The monoclonal antibody provides cell targeting specificity, as in the case demonstrated wherein the cells transfected carried the CD3 surface antigen (Discussion, page 139). As such, it is clear Hirsch et al. teach using the method with other antibodies to selectively target a cell population based on distinctive cell surface attributes.

Accordingly, Craig et al. anticipates the invention as now claimed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 250, 251, 271, 272, 273, and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirsch et al. (1993) *Transplantation Proceedings* 25:138-139 as applied to claims 246-249, 252, 255, 264, and 265 above, and further in view of Keating et al. (US Patent 6,503,755); Bos et al. (1992) *Hybridoma* 11:41-51; and Smith-Ravin et al. (1989) *Int. J. Radiat. Biol.* 56:951-961.

The claims read on linearized and nicked plasmids. The polynucleotide of claim 273 is hybridized; thus, the claims do not require a free, single stranded tail. Hirsch et al. is relied on for the reasons given above.

Hirsch et al. do not teach linearized plasmids or excluding the antibody to one strand or the other.

However, one of skill in the art at the time would reasonably have concluded that any method known in the art for coupling an antibody to a nucleic acid could be used in the method disclosed by Hirsch et al. for promoting cellular targeting and uptake. One of skill would further reasonably have concluded that constructs in which the antibody is coupled to one strand or both strands would have substantially the same properties and would produce substantially the same effects (MPEP 2144.09).

To the extent the antibodies localize the constructs to specific cell types, they serve cellular localization and cell targeting functions, as recited in the claims.

Additionally, the prior art taught that, under some conditions and depending on cell type, it may be preferable to linearize plasmid DNA prior to transfection of mammalian cells.

For example, Keating et al. taught improved methods for transfecting mammalian cells with plasmid DNA. It is taught that the plasmid DNA may be linearized prior to introduction into the cells, and that under some conditions linearized plasmid DNA can result in slightly higher transfection efficiencies relative to supercoiled DNA (col. 6, lines 27-36; Example 1, col. 10, lines 15-20; and see Examples 2 and 3).

Bos et al. echo Keating et al., teaching that the transfection efficiency of hybridoma cells with a plasmid, pSV2-neo, increased two-fold after linearization as compared to intact plasmid when using HEPES buffered Saline (see Abstract and Results).

Thus, it would have been obvious to one of skill at the time of invention to combine the antibody-mediated transfection method of Hirsch et al. with the linearization technique of Keating et al. or Bos et al. to further enhance the cell targeting and uptake of the plasmid DNA. The methods could have been combined with no significant or apparent change in their respective functions, wherein the antibody provides for cell targeting specificity and the linearization provides for enhanced uptake. Stated another way, it would have been obvious to apply the techniques of Keating et al. or Bos et al. to the antibody-coupled plasmids of Hirsch et al. to produce a linearized, antibody-conjugated plasmid with predictable properties.

The methods complement one another. As a result, the combination would have combined the benefits taught individually by Hirsch et al., Keating et al., and Bos et al. It would be the normal desire of any scientist in the field to achieve optimal transfection efficiency in the target cell population by applying those techniques, singly or in combination, known in the prior art to enhance plasmid DNA transfection.

With regard to claims 273-275, the prior art had taught the use of nicked or open circular plasmid DNA for the study of DNA repair mechanisms in mammalian cells. For example, see Smith-Ravin et al. (1989) *Int. J. Radiat. Biol.* 56:951-961, who used ionizing radiation to prepare open circular (i.e., nicked plasmid DNA) for transfection into chinese hamster ovary cells to study DNA repair mechanisms therein. It would have been obvious at the time of invention to use the method of Hirsch et al. to further enhance the uptake and delivery of such plasmids into any desired cell type to study DNA repair functions in any particular cell type.

Accordingly, the prior art had suggested the instantly claimed constructs.

***Response to Applicants' Arguments***

Applicants' arguments presented on 7/8/2008 not specifically addressed above are considered to be moot in view of the new rejections stated herein, above.

***Prior art made of record but not currently relied on***

The following prior art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Ramsay-Shaw et al. (US Patent 5,683,869) taught boranophosphate modified oligonucleotides for incorporation into DNA Vectors. The boranophosphate linkages are said to confer nuclease resistance. The modified vectors can be used for a variety of purposes including directed gene transfer and expression (col. 16, lines 15-45).

Putney et al. (1981) *Proc. Natl. Acad. Sci.* 78:7350-7354 taught methods for making and using phosphorothioate modified plasmid DNA.

Myers et al. (EP 0 273 085) taught methods for making and using polynucleotide-EGF conjugates for targeted transfection and/or transformation of mammalian cells.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, AU 1635
March 8, 2010